DETAILED ACTION

This Office Action is in response to Applicants' Amendment filed on 1 June 2009.

Claims 10-36 are pending in the instant application.

Claims 15-18, 24-27 and 33-36 were previously withdrawn from further consideration in the Office Action dated 27 February 2009 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 10-14, 19-23 and 28-32 are examined on its merits herein.

Priority

This application is a National Stage entry of PCT/EP2005/051364 filed on 23 March 2005 and claims priority to EPO foreign application 04101199.0 filed on 23 March 2004. A certified copy of the foreign priority document in English has been received.

Information Disclosure Statement

The information disclosure statement (IDS) dated 1 June 2009 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Rejections Withdrawn

Applicant's arguments, filed 1 June 2009, with respect to the rejection of claims 10-14, 19-23 and 28-32 under 35 USC § 103(a), as being unpatentable over journal publication by Nagahori *et al.*, in view of book publication by Silverman, has been fully considered and is persuasive because Silverman teaches elongation of carbon side chains in order to increase the lipophilicity of the molecule, which would permit the compound to penetrate into cell membranes. This is contrary to the instant invention wherein the compound binds to the pilus of free circulating bacteria. Thus, one of ordinary skill in the art would wish to avoid penetration of the compound into the cell membrane.

These rejections have been **withdrawn**.

The method of treating a subject suffering from an infection of a Gram-negative bacterium, said method comprising providing a subject suffering from an infection of a Gram-negative bacterium with a composition comprising n-heptyl α-D-mannose (R_1 = n-pentyl), is not fairly suggested in the prior art. Thus, the prior art search has been extended to include n-butyl α-D-mannose compounds (R_1 = ethyl).

The following are new ground(s) of rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

Claims 10-14 and 28-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a subject suffering from an infection of a Gram-negative bacterium, said method comprising unsubstituted linear alkyl α-D-mannose compounds, fluoro-substituted linear alkyl α-D-mannose compounds, p-nitrophenyl α-D-mannose, ethylphenyl α-D-mannose, ethyl-p-nitrophenyl α-D-mannose and p-aminophenyl α-D-mannose, does not reasonably provide enablement for a method of treating a subject suffering from an infection of a Gram-negative bacterium, said method comprising linear alkyl α-D-mannose compounds substituted with hydrophilic substituents, cyclohexyl α-D-mannose compounds, pyrimidyl cyclohexyl α-D-mannose compounds, and other substituted phenyl α-D-mannose compounds not mentioned above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or

unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected invention is drawn to a method of treating a subject suffering from an infection of a Gram-negative bacterium, said method comprising a number of different α-D-mannose compounds substituted with hydrophilic groups, cyclohexyl α-D-mannose compounds, or pyrimidyl α-D-mannose compounds.

Relative skill of those in the art: The relative skill of those in the art is high.

State of the prior art/Predictability or unpredictability of the art: Nagahori *et al.* (of record) teach that in designing a potential inhibitor of *E. coli* adhesion that is medically applicable, it is prudent to incorporate a long aliphatic chain or an aromatic residue immediately next to mannose. Furthermore, Bouckaert *et al.* teach an extensive hydrophobic patch surrounding the mannose-binding crevice (IDS dated 18 August 2008).

Amount of guidance/Existence of working examples: The instant specification provide sufficient data to show that unsubstituted linear alkyl α-D-mannose compounds, ethylphenyl mannose, ethylamino mannose, and p-nitrophenyl mannose are inhibitors in a binding assay based on the dissociation equilibrium. However, other than ethylamino mannose, there are **no** other working examples present which show that hydrophilic mannose compounds, pyrimidyl mannose compounds, or cyclohexyl mannose

compounds are inhibitory. The presence of one example for a hydrophilic substituent, ethylamino mannose, is not sufficient to show that all of the claimed hydrophilic compounds varying in location of hydrophilicity and charge density are inhibitory in view of the teachings of Nagahori *et al.* and Bouckaert *et al.* that the mannose binding crevice is surrounded my an extensive hydrophobic patch. Additionally, cyclohexyl compounds have an entirely different conformation from alkyl and aryl substituents of mannose compounds known to be inhibitory in the prior art. Thus one of skill in the art would be unable to predict whether such compounds are inhibitory.

Lack of a working example is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of a method of treating a subject suffering from an infection of a Gram-negative bacterium, said method comprising providing a subject suffering from an infection of a Gram-negative bacterium with a composition comprising hydrophilic mannose compounds, pyrimidyl mannose compounds, or cyclohexyl mannose compounds, as recited in the instant claims.

Genetech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors as discussed above, e.g., the amount of guidance provided, the predictability of the art and the lack of working examples, to

practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Written Description

Claims 19-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment with respect to amended claims herein has been fully considered but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for compounds wherein R_1 = n-heptyl or n-octyl. Claim 19 has been amended to include only compounds wherein R_1 = n-pentyl, n-hexyl, n-heptyl or n-octyl. However, the original specification does not support compounds wherein R_1 = n-heptyl or n-octyl. With regards to alkyl chains, the Specification only provides support for compounds wherein R_1 = n-ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl.

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that the Applicant was in possession of the invention as it is now claimed. See *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 111, CAFC 1991, see also *In re Winkhaus*, 188 USPQ 129, CCPA 1975.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagahori *et al.* (of record), in view of journal publication by Choudhury *et al.* (of record).

Nagahori *et al.* teach the inhibition of adhesion of type 1 fimbriated *Escherichia coli* to various mono-, di- and trivalent mannosides. Many bacteria, including pathogenic ones, express carbohydrate-specific adhesion on their fimbriae. These fimbrial adhesins are often implicated in the initial recognition/binding of bacteria to host cells or persisting colonization of bacteria on certain host cell surfaces. The mannose-

specific adhesion of type 1 fimbriated *E. coli* (known as the FimH protein) is known to cause common urinary tract infection (p. 836, column 1, paragraph 1). High-affinity ligands for these adhesins may be useful as therapeutics for preventing or mitigating pathological symptoms (p. 836, column 1, paragraph 2). Compounds that were tested for inhibition towards binding of ^{125}I-Man$_{21}$-ALK-HSA to *E. coli* include methyl-mannopyranoside, ethyl-mannopyranoside, p-nitrophenyl-mannopyranoside, as well as trivalent mannose compounds, divalent mannose compounds, neoglycoproteins, and dendrimers (p. 839, Table 3 and Table 4; p. 840 Table 5). The results of their study indicated that the presence of the α-mannose configuration enhances the affinity of the compound tremendously (p. 840, subheading "Discussion", paragraph 1). It appears that the β-oriented aglycon does not make good contact with the hydrophobic surface (p. 841, column 1, first full paragraph). The results also indicate that either a long aliphatic chain or an aromatic ring immediately next to the mannose sugar produces the best inhibitors (p. 836, paragraph 2). Nagahori *et al.* conclude that in designing a potential inhibitor of *E. coli* adhesion that is medically applicable, it is obviously prudent to incorporate a long aliphatic chain or an aromatic residue immediately next to mannose (p. 841, column 2, second full paragraph). The affinity can also be further enhanced by multivalency, such as by using dendrimers or neoglycoproteins.

Nagahori *et al.* do not explicitly teach the mannopyranoside species, butyl-α-D-mannopyranoside. However, as discussed above, Nagahori *et al.* do explicitly indicate that a potential inhibitor of *E. coli* adhesion that is medically applicable would

incorporate a long aliphatic chain or an aromatic residue immediately next to mannose (p. 841, column 2, second full paragraph).

Furthermore, Choudhury *et al.* teach an x-ray structure of the FimC-FimH chaperone-adhesin complex from uropathogenic *Escherichia coli*. The structure shows a pocket capable of accommodating a mono-mannose unit located at the tip of the FimH lectin domain (p. 1062, column 3; p. 1063, Fig. 1B). In an attempt to further understand the lectin-substrate binding, a molecule of cyclohexylbutanoyl-*N*-hydroxyethyl-D-glucamide (C-HEGA) is bound in the pocket (p. 1062, column 3; p. 1064, Fig. 3A). The C2, C3, C4 and C6 hydroxyl groups of C-HEGA are enclosed within the pocket, whereas the cyclohexylbutanoyl-N-hydroxyethyl groups point out from the pocket (p. 1062, column 3). These results indicate the importance of the C2, C3, C4 and C6 hydroxyl groups of mannose in binding, suggesting that alteration of these groups decreases binding and that alterations to the mannose structure can only be made at C1.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nagahori *et al.*, concerning medically applicable inhibitors of *E. coli* adhesion that incorporate an α-linked long aliphatic chain or an aromatic group at the anomeric position of mannose, with the teachings of Choudhury *et al.*, regarding the importance of the C2, C3, C4 and C6 hydroxyl groups of mannose in *E. coli* binding as deduced from the x-ray structure, thereby indicating that modifications to mannose can only be made at C1. It would have been *prima facie* obvious for a skilled artisan to use the information disclosed by Nagahori *et al.* and

Choudhury *et al.* to design a medically applicable inhibitor of *E. coli* adhesion that contains a long aliphatic chain at the anomeric position, such as n-butyl-α-D-mannopyranoside. Although Nagahori *et al.* do not disclose how long the length of the aliphatic chain should be, it would have been *prima facie* obvious for one of ordinary skill in the art to try successive homologs of the ethyl-α-D-mannopyranoside compound which was disclosed by Nagahori *et al.*, namely by extending the aliphatic carbon chain by one or two units, to propyl-α-D-mannopyranoside or butyl-α-D-mannopyranoside. Based on the teachings of Nagahori *et al.* that long aliphatic chains at the anomeric position can be good inhibitors of *E. coli* adhesion, one of ordinary skill in the art would expect that homologous extension of the aliphatic chain would result in inhibitors of *E. coli* adhesion that are better than the disclosed ethyl-α-D-mannopyranoside compound. Rather than generating random length chains of alkyl-α-D-mannopyranosides, such as by four or more carbon units, which may be unobvious since Nagahori *et al.* do not suggest how long the aliphatic chain should be, it would have been *prima facie* obvious for one of ordinary skill in the art to at least try a simple one or two carbon unit extension of ethyl-α-D-mannopyranoside. One of ordinary skill in the art would know that a composition comprising an *E. coli* adhesion inhibitor can thus be used in a method to treat a subject infected with uropathogenic *E. coli*, which is involved in urinary tract infection. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Nagahori *et al.*, that high affinity ligands for bacterial adhesins may be useful as therapeutics for preventing or mitigating pathological symptoms (p. 836, column 1, paragraph 2).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Applicants' data in Tables 1-3 of the instant Specification with respect to K_D values and $\Delta G°$ values of the various compounds, and the standard deviation values provided in the Declaration of Dr. Julie Bouckaert, submitted by Applicants on 16 December 2008 under 37 CFR § 1.132, have been considered. However, in view of the teachings of Nagahori *et al.* that long aliphatic chains at the anomeric position of α-D-mannopyranoside are potential inhibitors of *E. coli* adhesion, one of ordinary skill in the art would have been motivated to modify the ethyl-α-D-mannopyranoside disclosed in Nagahori *et al.* by extending the ethyl chain by one or two carbon units. Thus, the decrease observed in K_D values for butyl-α-D-mannopyranoside is not unexpected in view of the teachings of Nagahori *et al.* Furthermore, a K_d of 1200 for ethylman with a SD of 235 is not considered to be statistically significant from a a K_d of 151 for butylman with a SD of 16.8, particularly in the absence of any p-values.

Section [0002]

Claims 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagahori *et al.* (of record), in view of journal publication by Choudhury *et al.* (of record), in view of journal publication by Nicotra *et al.* (PTO-892, Ref. U).

The teachings of Nagahori *et al.* were as described in section [0001] above in the claim rejections under 35 USC § 103.

Nagahori *et al.* do not explicitly teach the mannopyranoside species, butyl-α-D-mannopyranoside with a C-linkage. However, as discussed above, Nagahori *et al.* do explicitly indicate that a potential inhibitor of *E. coli* adhesion that is medically applicable would incorporate a long aliphatic chain or an aromatic residue immediately next to mannose (p. 841, column 2, second full paragraph).

Furthermore, Choudhury *et al.* teach an x-ray structure of the FimC-FimH chaperone-adhesin complex from uropathogenic *Escherichia coli*, as discussed in section [0001] above in the claim rejections under 35 USC § 103.

Additionally, Nicotra *et al.* teach that C-glycosides are of biological interest as potential inhibitors of carbohydrate processing enzymes and as stable analogs of glycoforms involved in cellular recognition, such as adhesion of the cells with viruses, bacteria, toxins and tumor cells (p. 58, first full paragraph). The modification of O-glycosides to C-glycosides compromise the anomeric reactivity of the sugar, giving rise to antimetabolites that can inhibit carbohydrate processing enzymes (p. 55, abstract). Thus, the possibility of interfering in the different cell-cell and cell-pathogen adhesion processes, employing stable analogs of the metabolic intermediates, or mimics of the receptor recognized glycoforms, have stimulated interest in C-glycosides (p. 58-59, sections 2.1 and 2.2).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nagahori *et al.*, concerning medically applicable inhibitors of *E. coli* adhesion that incorporate an α-linked long aliphatic chain or an aromatic group at the anomeric position of mannose, with the teachings of

Choudhury *et al.*, regarding the importance of the C2, C3, C4 and C6 hydroxyl groups of mannose in *E. coli* binding as deduced from the x-ray structure, thereby indicating that modifications to mannose can only be made at C1, with the teachings of Nicotra *et al.*, regarding C-glycosides as stable mimics of receptor recognized glycoforms. It would have been *prima facie* obvious for a skilled artisan to use the information disclosed by Nagahori *et al.* and Choudhury *et al.* to design a medically applicable inhibitor of *E. coli* adhesion that contains a long aliphatic chain at the anomeric position, such as n-butyl-α-D-mannopyranoside. One of ordinary skill in the art would have been further motivated to modify the mannose O-linked alkyl chain to a mannose C-linked alkyl chain, in order to receive the expected benefit, as suggested by Nicotra *et al.*, that C-glycoside mimics of receptor recognized glycoforms can interfere in cell-pathogen adhesion processes. Although Nagahori *et al.* do not disclose how long the length of the aliphatic chain should be, it would have been *prima facie* obvious for one of ordinary skill in the art to try successive homologs of the ethyl-α-D-mannopyranoside compound which was disclosed by Nagahori *et al.*, namely by extending the aliphatic carbon chain by one or two units, to propyl-α-D-mannopyranoside or butyl-α-D-mannopyranoside. Based on the teachings of Nagahori *et al.* that long aliphatic chains at the anomeric position can be good inhibitors of *E. coli* adhesion, one of ordinary skill in the art would expect that homologous extension of the aliphatic chain would result in inhibitors of *E. coli* adhesion that are better than the disclosed ethyl-α-D-mannopyranoside compound. Rather than generating random length chains of alkyl-α-D-mannopyranosides, such as by four or more carbon units, which may be unobvious since Nagahori *et al.* do not

suggest how long the aliphatic chain should be, it would have been *prima facie* obvious for one of ordinary skill in the art to at least try a simple one or two carbon unit extension of ethyl-α-D-mannopyranoside. One of ordinary skill in the art would know that a composition comprising an *E. coli* adhesion inhibitor can thus be used in a method to treat a subject infected with uropathogenic *E. coli*, which is involved in urinary tract infection. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Nagahori *et al.*, that high affinity ligands for bacterial adhesins may be useful as therapeutics for preventing or mitigating pathological symptoms (p. 836, column 1, paragraph 2). Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Conclusion

No claim is allowed. This rejection is made NON-FINAL due to the new/modified grounds of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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